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先天性唇瘘畸形的相关研究进展

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摘　要

先天性唇瘘是一种极其罕见的先天性畸形，大多发生在下唇，发生在上唇者少见。患者多因局部不适或美容需求而就诊，由于先天性唇瘘畸形发生率极低，且部分患者无明显临床表现，往往容易被患者或临床医生忽视，但该畸形可与多种罕见的遗传性疾病相关联，临床医生认识该畸形对于为患者提供更好的治疗方式和可能的遗传咨询具有重要意义。本文就这先天性唇瘘的流行病学、临床表现、解剖特征、相关疾病和治疗方法等进行综述。

关键词

唇瘘，先天性畸形，发育异常，基因

Research Progress of Congenital Lip Sinus

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Abstract

Congenital lip sinus is a rare congenital deformity, predominantly occurring in the lower lip with less frequency in the upper lip. Patients often seek medical attention due to local discomfort or concerns about appearance. Due to its low incidence rate and the fact that some patients may lack obvious clinical manifestations, this condition is often overlooked. However, congenital lip sinus can be associated with various genetic diseases. Understanding this anomaly is of paramount importance for providing better treatment options and possible genetic counseling for patients. This

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article reviews the relevant research progress.

Keywords

Lip Sinus, Congenital Abnormalities, Dysplasia, Genes

1. 引言

先天性唇瘘(Congenital Lip Sinus)，又称唇凹或唇窦道，是一种罕见的先天性畸形，多位于下唇，下唇瘘(Lower Lip Sinus)常与范德沃德综合征(Van der Woude syndrome)等遗传性疾病相关，上唇少见[1]，位于唇系带也有过报道[2]。Demarquay 在 1845 年首次报道了先天性唇瘘[3]。先天性唇瘘的畸形通常较轻微[4] [5]，孤立的先天性唇瘘可无明显症状[4] [6]，也可伴随分泌物或反复感染后出现红肿、疼痛等症状[1] [4] [7] [8]。手术切除病灶是目前主要的治疗方式[8] [9]。该病在国内鲜有报道，临床上对此病的认识相对缺乏，现就先天性唇瘘的流行病学、临床表现、解剖特征、相关疾病和治疗方法等进行综述。

2. 流行病学

目前关于先天性唇瘘的总体流行病学特点尚无确切结论。以“唇瘘/唇凹/唇窦”为关键词在中国知网(https://www.cnki.net/)中检索出相关文献 29 篇，共计病例数不超过 130，其中上唇瘘不超过 10 例。相关文献表明下唇瘘在人群中的发病率约为 0.001%，也有文献表明下唇瘘在人群中的发病率约为 0.00001%，而上唇瘘则更为罕见[1] [8] [9] [10]。Aoki 等人根据先天性上唇瘘(Congenital Upper Lip Sinus)的病灶位置及是否伴随其他畸形将其分为三种类型，I 型为上唇中线瘘(Midline Sinus of The Upper Lip)不伴其他畸形，女性占比较大；II 型为上唇中线瘘伴随其他畸形，如唇裂、轻度眼距增宽、上唇系带异常、皮罗氏序列征(Pierre Robin Sequence)等，男女分布较均匀；III 型为上唇外侧瘘(Upper Lip Lateral Sinus)伴或不伴其他畸形[1]。目前有关上唇中线瘘的报道不超过 70 例[11]。Fok 等人通过对 16 例上唇瘘病例的回顾发现，大多数上唇瘘患者是亚洲人[8]。Chowdhary 等人通过对 35 例上唇瘘病例的回顾同样也发现大多数患者为亚洲人，且女性居多[4]。1998 年，朱光辉等人报道了 8 例先天性唇瘘，8 例患者均伴有其他畸形(唇/腭裂、前牙反颌、眶距增宽、侧切牙缺失等)，其中 2 例下唇瘘患者的父母均患唇腭裂及唇瘘，1 例上唇瘘患者的母亲在妊娠期间有苯海拉明、扑尔敏等药物服用史[7]。然而，由于基数较小，尚不能进行结论性分析，仍需进一步的流行病学研究。

3. 临床表现、解剖特征及病因

先天性唇瘘即有一个开口的窦道[2] [7] [12]。孤立的先天性唇瘘通常无明显症状[4] [6]，也可伴随分泌物或反复感染后出现红肿、疼痛等症状[4] [13]。

先天性上唇瘘，即出现在上唇的窦道。瘘口在上唇中线或两侧，其中上唇中线瘘全球范围内仅报道不到 70 例患者[11]，Kun-Darbois 等人通过回顾文献指出 I 型上唇瘘(上唇中线瘘不伴其他畸形)占比 47.5%，其次是 II 型(上唇中线瘘伴随其他畸形)占比 30%，最后是 III 型(上唇外侧瘘伴或不伴其他畸形)占比 22.5% [9]。先天性上唇瘘可孤立出现[5] [8] [13]，可无明显症状[8] [9]，也可伴随唇裂、轻度眼距增宽、上唇系

带异常、皮罗氏序列征等畸形[1]。瘘口见于皮肤黏膜，盲端向下到达口轮匝肌，通常与口腔没有联系[1] [10]。其形成的机制尚不清楚，目前主要存在三种假说，内陷理论(Invagination Theory)：上唇瘘的形成是由于前鼻突(Frontonasal Process)形成的过程中鼻板(Nasal Placodes)的外胚层内陷失败所导致；合并理论(Merging Theory)：上唇瘘的形成是由于间充质干细胞不足引起正常间充质干细胞合并过程出现异常而导致；融合理论(Fusion Theory)：上唇瘘的形成是由于前鼻突和上颌突(Maxillary Processes)的不完全融合导致[1] [8] [9] [11]。

先天性下唇瘘，即出现在下唇的窦道。可以表现为圆形、椭圆形、横线形、裂隙样或沟壑样[14]。瘘管深度通常为1~25毫米，可以是无症状的轻微凹陷，也可穿至唾液腺导致瘘口排出唾液，瘘口直径由小于头发粗细至6毫米不等[2] [6] [14]-[17]。下唇瘘通常成对出现，对称分布在下唇中线两侧，通常相距1 cm，也可位于单侧(左侧多见)、中间或不对称地分布于两侧，也可单个出现[2] [15] [18]。下唇瘘可以作为一种孤立的缺陷出现[5] [8] [13]，也可与多种疾病相关，如范德沃德综合征、腘窝翼状蹼综合征(Popliteal Ptergium Syndrome, PPS)、歌舞伎面谱综合征(Kabuki syndrome)、口－面－指综合征(Oral-Facial-Digital Syndrome, OFD)等[5] [14] [19]。最近的一种假说对下唇瘘的形成进行了推测：在头颈发育阶段的5.5周时，下颌弓(Mandibular Arch)和下唇侧沟(Sulcus Lateralis of The Lower Lip)发生融合，而上颌突和前鼻突的融合则发生在6周左右，据推测，可能存在一种共同事件同时影响了这两个部位的融合[5] [14]。但其确切机制目前仍不清楚。

4. 相关疾病

先天性唇瘘孤立存在时通常无明显症状[4]-[6] [8] [16] [17] [19]。但先天性唇瘘也可能是某些疾病的临床表现，如范德沃德综合征、腘窝翼状蹼综合征、歌舞伎面谱综合征、口－面－指综合征等。

4.1. 范德沃德综合征

范德沃德综合征是一种罕见的常染色体显性遗传性疾病，Van der Woude在1954年详细研究了五个家系后，发现下唇瘘与唇裂和腭裂的组合是由某种基因引起的，这种综合征后来被命名为范德沃德综合征[20]。由位于染色体1q32-q41上的IRF6基因突变导致，染色体1p34的异常也与范德沃德综合征相关，GRHL3基因突变也被报道过可致范德沃德综合征[14] [16] [18] [21]-[23]。该综合征在一般人群中患病率约为1/100,000~1/75,000，外显率80%~100%，但表现度有明显差异，即在不同家系的患者中，甚至同一家系内的不同患者，其临床表现往往也不尽相同[17] [21] [24]。其中，88%的患者伴有唇瘘，64%的患者仅表现为唇瘘，21%的患者伴有唇裂/腭裂，下唇瘘合并唇裂/腭裂的发生率约为80% [18] [24] [25]。其他症状包括马蹄内翻足、并指/趾、先天缺牙、泌尿生殖系统异常、心血管异常、眼睑粘连、四肢畸形、慢性中耳炎、两岐悬雍垂、智力低下等[2] [5] [20] [21] [26]。

4.2. 腘窝翼状蹼综合征

腘窝翼状蹼综合征是一种罕见的常染色体显性遗传性疾病[27]。最早于1869年由Trelat描述，Gorlin等人于1968年基于腘窝翼状赘皮的罕见症状而将其命名为腘窝翼状蹼综合征[27] [28]。位于染色体1q32-q41上的IRF6基因是其致病基因[28]，另染色体21q22.3上的RIPK4基因突变被确定为遗传方式为常染色体隐性遗传的腘窝翼状蹼综合征的病因，又称作巴索卡斯-帕帕斯综合征(Bartsocas-Papas Syndrome) [29] [30]。该综合征的发病率约为1/300,000 [28] [31]。但存在不完全外显，且其表现度具有差异性[31]。腘窝翼状蹼综合征中最常见的体征是腭裂伴或不伴唇裂，发生率为91%~97%，唇裂的发生率为58%，下唇瘘的发生率为45.6%，腘窝蹼状皱褶发生率58%，并指/趾发生率50%，泌尿生殖系统异常发生率37%，

指甲畸形发生率 33% [29]。其他畸形包括眼睑粘连、畸形足、上下腭弓纤维束粘连导致的连腭畸形等，患者的智力和生长发育通常不受影[2] [5] [20] [21] [26] [29] [31]。满足唇裂/腭裂、腘窝蹼状皱褶、下唇瘘、生殖器和指甲畸形四条中的任意三条即可诊断腘窝翼状蹼综合征[32]。

4.3. 歌舞伎化妆综合征

歌舞伎化妆综合征是一种罕见的遗传性疾病，最早由日本学者 Niikawa 等人和 Kuroki 等人于 1981 年同时报道[33] [34]。大约 70%的患者存在 KMT2D 或 KDM6A 基因突变[35]。其在所有种族中发病率约为 1/32,000~1/86,000 [36] [37]。该病典型的特征有五个：(1) 特殊面容(100%)：眼睑外翻、长睑裂，弓形眉、外侧三分之一眉毛稀疏、鼻中隔短、鼻尖扁平、耳大而突出、唇裂/腭裂等；(2) 骨骼异常(92%)：第 5 手指很短，脊柱畸形，椎体矢状裂等；(3) 皮纹异常(93%)：小鱼际区箕形纹增多，指纹三角的 c 或 d 缺失，持续存在的胎儿指尖垫等；(4) 轻中度智力障碍(92%)；(5) 发育迟缓(83%) [37] [38]。其他相关异常包括心脏异常(室间隔缺损、主动脉缩窄、房间隔缺损、动脉导管未闭等)、免疫缺陷和自身免疫性疾病(免疫性血小板减少性紫癜、肾小球肾炎等)、慢性中耳炎、中枢神经系统畸形、泌尿生殖系统畸形(隐睾、马蹄肾、肾发育不全等)、进食困难、肛门直肠畸形、下唇瘘等[36] [37] [39]-[42]。唇瘘在歌舞伎化妆综合征患者中极其少见。Kokitsu-Nakata 等人于 1999 年报道了 1 例伴随下唇瘘的歌舞伎化妆综合征患者[41]，Shotelersuk 等人于 2002 年报道了 3 例伴随下唇瘘的歌舞伎化妆综合征患者[42]，Abdel-Salam 等人于 2008 年报道了 1 例伴随下唇瘘的歌舞伎化妆综合征患者[40]，David-Paloyo 等人于 2014 年报道了 2 例伴随下唇瘘的歌舞伎化妆综合征患者[36]，Murakami 等人于 2020 年报道了 2 例伴随下唇瘘的歌舞伎化妆综合征患者[43]。

4.4. 口－面－指综合征

口－面－指综合征是一种主要表现为口腔异常、面部及指/趾畸形的罕见遗传性疾病[44]。1941 年首次被报道[45]。共有 14 种临床分型和 2 种未分类的亚型，其中以 I 型(OFD-I)最为常见，OFD-I 呈 X 连锁显性遗传，OFD-I 基因是其致病基因，发病率约为 1/250,000~1/50,000 [46] [47]。另有相关报道口－面－指综合征存在 X 连锁隐性遗传和常染色体隐性遗传，目前仍有 40%的口－面－指综合征的致病基因未知[48]。该综合征的典型特征是 (1) 口腔畸形：舌错构瘤、腭裂、分叶舌、上唇正中裂、口腔系带增生等；(2) 颅面部畸形：宽眼距、宽鼻根、鼻尖扁平、面部不对称、鼻翼软骨发育不全、头发稀疏且干燥等；(3) 骨骼异常：并指/趾、多指/趾等；(4) 40%~60%的患者具有中枢神经系统异常，如脑结构异常、智力障碍等[44] [46] [48] [49]。Salinas 等人于 1991 年报道过一例伴随下唇瘘的 OFD-I 患者[50]。

此外，Grenman 等人在 1985 年报道过一例伴随上唇中线瘘的皮罗氏序列征患者[51]。Baker 通过对 3283 名高加索男性的调研后表明唇瘘患者同时发生耳前瘘管的概率约为 3.8%，耳前瘘管与唇瘘之间存在显著相关性[52] [53]。Marres 和 Cremers 在 1991 报道了一种以先天传导性或混合性耳聋、耳前瘘管、唇瘘和外耳异常等为主要畸形的遗传性疾病，部分文献中将其称为 Marres-Cremers 综合征[5] [14]。Donnell 等人曾报道过一例伴随上唇中线瘘的鼻背中线皮样囊肿，该病变存在颅内延伸可能，此前存在颅内延伸的伴随上唇中线瘘的鼻背中线皮样囊肿仅报道过 2 例[54]。

5. 治疗

先天性唇瘘可以孤立存在，如不引起明显的临床问题，则无需特殊治疗[4]-[6] [8] [16] [17] [19]。如果存在反复分泌液体或红肿、疼痛等症状，或出于美容需求，需行手术切除瘘管[5] [21]。手术在局麻或全麻下进行，术中在瘘管内注射少许亚甲蓝，使整个管壁着色，再插入泪道探针，在瘘口周围作梭形切

口，沿泪道探针剥离瘘管至末端，完整切除瘘管后严密缝合手术创面，若存在反复分泌唾液，所有附着的粘液腺应连同瘘管一并切除，以防术后形成黏液囊肿，分层关闭创面时，注意肌层缝合，以免术后患区凹陷[5] [13] [16] [21]。也有文献记录经唇颊龈沟入路切除瘘管，沿相反的方向切除整个瘘管，只做一个以瘘口为中心的小椭圆形皮肤切口，其优点是将皮肤切口最小化[8]。

6. 总结

对于罕见的先天性畸形，即使是那些在临床上看似无关紧要的畸形，例如本文中提到的先天性唇瘘，也需要研究其潜在原因。这有助于促进该领域的进步，同时也使得临床医生能够独立对相关畸形进行更准确的评估。唇瘘还同多种疾病相关，提高对唇瘘的认识，有利于对患者进行更加完善的治疗，提供准确的遗传咨询。

参考文献

[1] Aoki, M., Sakamoto, Y., Nagasao, T., *et al*. (2014) Classification of Congenital Midline Upper Lip Sinuses: A Case Report and Review of the Literature. *The Cleft Palate Craniofacial Journal*, **51**, 154-157. https://doi.org/10.1597/12-046r

[2] Ortega-Resinas, M., Sanchez-Conejo-Mir, J., Sanchez-Pedreño-Guillen, P., *et al*. (1984) Congenital Fistulas of the Lower Lip. Radiographic Evaluation. *Dermatologica*, **169**, 359-362. https://doi.org/10.1159/000249628

[3] Macomber, W. and Wang, M. (1956) Congenital Lip Sinuses. *Plastic and Reconstructive Surgery*, **18**, 319-328. https://doi.org/10.1097/00006534-195611000-00001

[4] Chowdhary, F., Chowdhary, A., Chowdhary, Z., *et al*. (2019) Midline Congenital Upper Lip Sinus: A Rare Case. *Indian Journal of Otolaryngology and Head & Neck Surgery*, **71**, 553-557. https://doi.org/10.1007/s12070-018-1399-z

[5] Manoharan, G.V.M.G.I., Singh, K. and Reghu, P. (2013) Congenital Lower Lip Pits—Report of a Rare Case. *International Journal of Medical & Dental Case Reports*, **3**, 146-150.

[6] Rintala, A., Lahti, A. and Gylling, U. (1970) Congenital Sinuses of the Lower Lip in Connection with Cleft Lip and Palate. *The Cleft Palate Journal*, **7**, 336-346.

[7] 朱光辉, 濮礼臣, 金惠玲, 等. 先天性唇瘘 8 例报告[J]. 现代口腔医学杂志, 1998(12): 109.

[8] Fok, D., Kua, E.H. and Por, Y.C. (2015) Congenital Midline Sinus of the Upper Lip. *Singapore Medical Journal*, **56**, E107-E109.

[9] Kun-Darbois, J.D., Chatellier, A., Pare, A., *et al*. (2018) Congenital Midline Upper Lip Sinuses: 3 Rare Cases. *The Cleft Palate Craniofacial Journal*, **55**, 292-295. https://doi.org/10.1177/1055665617723635

[10] Xu, Y., Chen, R., Mu, Y., *et al*. (2016) Congenital Midline Sinus of the Upper Lip. *Journal of Craniofacial Surgery*, **27**, 1306-1307. https://doi.org/10.1097/SCS.0000000000002568

[11] Kotowski, M. and Szydlowski, J. (2023) Congenital Midline Upper Lip Sinuses with Intracranial Extension—A Variant of Nasal Dermoid? An Embryology-Based Concept. *International Journal of Pediatric Otorhinolaryngology*, **164**, Article 111394. https://doi.org/10.1016/j.ijporl.2022.111394

[12] Asahina, I., Sakakibara, T., Miyashin, M., *et al*. (1997) Congenital Midline Sinus of the Upper Lip: Case Report and Review of Literature. *The Cleft Palate Craniofacial Journal*, **34**, 83-85. https://doi.org/10.1597/1545-1569_1997_034_0083_cmsotu_2.3.co_2

[13] Zarandy, M.M., Givehchi, G. and Mohammadi, M. (2005) A Familial Occurrence of Lip Anomaly. *American Journal of Otolaryngology*, **26**, 132-134. https://doi.org/10.1016/j.amjoto.2004.06.018

[14] Hambire, C. and Hambire, U. (2019) Nonsyndromic Familial Congenital Lower Lip Pits. *Contemporary Clinical Dentistry*, **10**, 664-667. https://doi.org/10.4103/ccd.ccd_120_19

[15] Rizos, M. and Spyropoulos, M. (2004) Van der Woude Syndrome: A Review. Cardinal Signs, Epidemiology, Associated Features, Differential Diagnosis, Expressivity, Genetic Counselling and Treatment. *European Journal of Orthodontics*, **26**, 17-24. https://doi.org/10.1093/ejo/26.1.17

[16] Angiero, F., Farronato, D., Ferrante, F., *et al*. (2018) Clinical, Histomorphological and Therapeutic Features of the Van der Woude Syndrome: Literature Review and Presentation of an Unusual Case. *European Journal of Paediatric Dentistry*, **19**, 70-73.

[17] Shprintzen, R., Goldberg, R. and Sidoti, E. (1980) The Penetrance and Variable Expression of the Van der Woude

Syndrome: Implications for Genetic Counseling. *The Cleft Palate Journal*, **17**, 52-57.

[18] Dissemond, J., Haberer, D., Franckson, T., *et al*. (2004) The Van der Woude Syndrome: A Case Report and Review of the Literature. *Journal of the European Academy of Dermatology and Venereology*, **18**, 611-613. https://doi.org/10.1111/j.1468-3083.2004.00996.x

[19] Neale, H., Blundell, A.R., Schmidt, B., *et al*. (2021) Solitary Congenital Lip Pit in an Infant. *Pediatric Dermatology*, **38**, 1363-1365. https://doi.org/10.1111/pde.14724

[20] Lekkas, C., Latief, B. and Corputty, J. (1998) Median Cleft of the Lower Lip Associated with Lip Pits and Cleft of the Lip and Palate. *The Cleft Palate Craniofacial Journal*, **35**, 269-271. https://doi.org/10.1597/1545-1569_1998_035_0269_mcotll_2.3.co_2

[21] Gurpal-Chhabda, V. and Singh-Chhabda, G. (2018) Congenital Lower Lip Pits: Van der Woude Syndrome. *Journal of Clinical and Experimental Dentistry*, **10**, e1127-e1129. https://doi.org/10.4317/jced.54953

[22] Kondo, S., Schutte, B.C., Richardson, R.J., *et al*. (2002) Mutations in IRF6 Cause Van der Woude and Popliteal Pterygium Syndromes. *Nature Genetics*, **32**, 285-289. https://doi.org/10.1038/ng985

[23] Katsube, M., Yoshiura, K. and Kusumoto, K. (2015) A Japanese Family with Popliteal Pterygium Syndrome. *Case Reports in Plastic Surgery and Hand Surgery*, **2**, 50-52. https://doi.org/10.3109/23320885.2015.1038347

[24] Calista, D. (2002) Congential Lower Lip Pits. *Pediatric Dermatology*, **19**, 363-364. https://doi.org/10.1046/j.1525-1470.2002.00099.x

[25] Van Der Woude, A. (1954) Fistula Labii Inferioris Congenita and Its Association with Cleft Lip and Palate. *The American Journal of Human Genetics*, **6**, 244-256.

[26] 黄长波, 阎寒松, 陈昕, 等. 一个范德伍德综合征家系的 IRF6 基因突变检测[J]. 口腔医学研究, 2006, 22(3): 322-325.

[27] 孙一丹, 孙晓晗, 曲辉, 等. 1 例腘窝翼状蹼综合征患儿及家属 IRF6 基因突变的检测[J]. 中国实用儿科杂志, 2022, 37(11): 861-864.

[28] Gahm, C., Kuylenstierna, R. and Papatziamos, G. (2007) Popliteal Pterygium Syndrome (PPS) with Intra-Alveolar Syngnathia: A Discussion of Anesthetic and Surgical Considerations. *International Journal of Pediatric Otorhinolaryngology*, **71**, 1613-1616. https://doi.org/10.1016/j.ijporl.2007.05.024

[29] Qasim, M. and Shaukat, M. (2012) Popliteal Pterygium Syndrome: A Rare Entity. *APSP Journal of Case Reports*, **3**, Article No. 5.

[30] Kalay, E., Sezgin, O., Chellappa, V., *et al*. (2012) Mutations in *RIPK4* Cause the Autosomal-Recessive Form of Popliteal Pterygium Syndrome. *The American Journal of Human Genetics*, **90**, 76-85. https://doi.org/10.1016/j.ajhg.2011.11.014

[31] Sisti, A., Freda, N., Giacomina, A., *et al*. (2017) Popliteal Pterygium Syndrome with Syngnathia. *Journal of Craniofacial Surgery*, **28**, e250-e251. https://doi.org/10.1097/SCS.0000000000003473

[32] Escobar, V. and Weaver, D. (1978) Popliteal Pterygium Syndrome: A Phenotypic and Genetic Analysis. *Journal of Genetic Medicine*, **15**, 35-42. https://doi.org/10.1136/jmg.15.1.35

[33] Niikawa, N., Matsuura, N., Fukushima, Y., *et al*. (1981) Kabuki Make-Up Syndrome: A Syndrome of Mental Retardation, Unusual Facies, Large and Protruding Ears, and Postnatal Growth Deficiency. *The Journal of Pediatrics*, **99**, 565-569. https://doi.org/10.1016/S0022-3476(81)80255-7

[34] Kuroki, Y., Suzuki, Y., Chyo, H., *et al*. (1981) A New Malformation Syndrome of Long Palpebral Fissures, Large Ears, Depressed Nasal Tip, and Skeletal Anomalies Associated with Postnatal Dwarfism and Mental Retardation. *The Journal of Pediatrics*, **99**, 570-573. https://doi.org/10.1016/S0022-3476(81)80256-9

[35] Adam, M.P., Banka, S., Bjornsson, H.T., *et al*. (2019) Kabuki Syndrome: International Consensus Diagnostic Criteria. *Journal of Medical Genetics*, **56**, 89-95. https://doi.org/10.1136/jmedgenet-2018-105625

[36] David-Paloyo, F.P., Yang, X., Lin, J.L., *et al*. (2014) Lower Lip Pits: Van der Woude or Kabuki Syndrome? *The Cleft Palate Craniofacial Journal*, **51**, 729-734. https://doi.org/10.1597/12-258

[37] Barry, K.K., Tsaparlis, M., Hoffman, D., *et al*. (2022) From Genotype to Phenotype—A Review of Kabuki Syndrome. *Genes*, **13**, Article 1761. https://doi.org/10.3390/genes13101761

[38] Niikawa, N., Kuroki, Y., Kajii, T., *et al*. (1988) Kabuki Make-Up (Niikawa-Kuroki) Syndrome: A Study of 62 Patients. *American Journal of Medical Genetics*, **31**, 565-589. https://doi.org/10.1002/ajmg.1320310312

[39] Wang, Y.R., Xu, N.X., Wang, J., *et al*. (2019) Kabuki Syndrome: Review of the Clinical Features, Diagnosis and Epigenetic Mechanisms. *World Journal of Pediatrics*, **15**, 528-535. https://doi.org/10.1007/s12519-019-00309-4

[40] Abdel-Salam, G., Afifi, H., Eid, M., *et al*. (2008) Anorectal Anomalies, Diaphragmatic Defect, Cleft Palate, Lower Lip Pits, Hypopigmentation and Hypogammaglobulinemia A in Kabuki Syndrome: A Rare Combination. *Journal of Ge-*

netic Counseling, **19**, 309-317.

[41] Kokitsu-Nakata, N., Vendramini, S. and Guion-Almeida, M. (1999) Lower Lip Pits and Anorectal Anomalies in Kabuki Syndrome. *American Journal of Medical Genetics*, **86**, 282-284. https://doi.org/10.1002/(SICI)1096-8628(19990917)86:3%3C282::AID-AJMG17%3E3.0.CO;2-Q

[42] Shotelersuk, V., Punyashthiti, R., Srivuthana, S., *et al*. (2002) Kabuki Syndrome: Report of Six Thai Children and Further Phenotypic and Genetic Delineation. *American Journal of Medical Genetics*, **110**, 384-390. https://doi.org/10.1002/ajmg.10474

[43] Murakami, H., Tsurusaki, Y., Enomoto, K., *et al*. (2020) Update of the Genotype and Phenotype of *KMT2D* and *KDM6A* by Genetic Screening of 100 Patients with Clinically Suspected Kabuki Syndrome. *The American Journal of Medical Genetics-Part A*, **182**, 2333-2344. https://doi.org/10.1002/ajmg.a.61793

[44] Minervini, G., Romano, A., Petruzzi, M., *et al*. (2018) Oral-Facial-Digital Syndrome (OFD): 31-Year Follow-Up Management and Monitoring. *Journal of Biological Regulators and Homeostatic Agents*, **32**, 127-130.

[45] Franco, B. and Thauvin-Robinet, C. (2016) Update on Oral-Facial-Digital Syndromes (OFDS). *Cilia*, **5**, Article No. 12. https://doi.org/10.1186/s13630-016-0034-4

[46] 程青青, 楚伟, 霍平, 等. 口-面-指综合征一个家系的表型与遗传学分析[J]. 中华医学遗传学杂志, 2023, 40(2): 208-212.

[47] Azukizawa, T., Yamamoto, M., Narumiya, S., *et al*. (2013) Oral-Facial-Digital Syndrome Type 1 with Hypothalamic Hamartoma and Dandy-Walker Malformation. *Pediatric Neurology*, **48**, 329-332. https://doi.org/10.1016/j.pediatrneurol.2012.12.016

[48] Strong, A., Simone, L., Krentz, A., *et al*. (2021) Expanding the Genetic Landscape of Oral-Facial-Digital Syndrome with Two Novel Genes. *The American Journal of Medical Genetics-Part A*, **185**, 2409-2416. https://doi.org/10.1002/ajmg.a.62337

[49] Bruel A, L., Franco, B., Duffourd, Y., *et al*. (2017) Fifteen Years of Research on Oral-Facial-Digital Syndromes: From 1 to 16 Causal Genes. *Journal of Medical Genetics*, **54**, 371-380. https://doi.org/10.1136/jmedgenet-2016-104436

[50] Salinas, C., Pai, G., Vera, C., *et al*. (1991) Variability of Expression of the Orofaciodigital Syndrome Type I in Black Females: Six Cases. *American Journal of Medical Genetics*, **38**, 574-582. https://doi.org/10.1002/ajmg.1320380416

[51] Grenman, R., Salo, H. and Rintala, A. (1985) Midline Sinuses of the Upper Lip: Case Report. *Scandinavian Journal of Plastic and Reconstructive Surgery*, **19**, 215-219. https://doi.org/10.3109/02844318509072379

[52] Baker, B. (1966) Pits of the Lip Commissures in Caucasoid Males. *Oral Surgery, Oral Medicine, Oral Pathology*, **21**, 56-60. https://doi.org/10.1016/0030-4220(66)90014-4

[53] Marres, H. and Cremers, C. (1991) Congenital Conductive or Mixed Deafness, Preauricular Sinus, External Ear Anomaly and Commissural Lip Pits: An Autosomal Dominant Inherited Syndrome. *Annals of Otology, Rhinology & Laryngology*, **100**, 928-932. https://doi.org/10.1177/000348949110001113

[54] Donnell, C.C., McKeague, K.F., Cooper, A., *et al*. (2020) Nasofrontal Dermoid Cyst: Rare Presentation of a Philtrum Sinus. *British Journal of Oral and Maxillofacial Surgery*, **58**, 608-610. https://doi.org/10.1016/j.bjoms.2020.03.004